What is claimed is:

1. A non-human transgenic animal capable of producing heterologous T-cell receptors, comprising:

inactivated endogenous T-cell receptor loci; and

transgenes contained within its genome composed of human T-cell receptor loci.

2. The non-human transgenic animal of claim 1, wherein said inactivated endogenous T-cell receptor loci are α and β chain T-cell receptor loci.

3. The non-human transgenic animal of claim 1 or 2, wherein said human T-cell receptor loci are unrearranged.

4. The non-human transgenic animal of one of claims 1-3, wherein said human T-cell receptor loci are composed, in operable linkage, of a plurality of human T-cell receptor V genes, and D and /or J and C genes.

5. The non-human transgenic animal of one of claims 1-4, wherein said animal is capable of productive VDJC rearrangement and expressing heterologous T-cell receptors.

6. The non-human transgenic animal of any one of claims 1-5, wherein said transgenes undergo productive VDJC rearrangement in lymphocytes of said non-human transgenic animal and wherein T-cells express detectable amounts of transgenic TCR in response to antigenic stimulation.

7. The non-human transgenic animal of any one of claims 1-6 wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to an antigen and wherein the T-cell receptors comprise a human T-cell receptor.

8. The non-human transgenic animal of any one of claims 1-7 wherein a produced human T-cell receptor is composed of human α and β chains.

9. The non-human transgenic animal of any one of the preceding claims, further comprising:

transgenes contained within its genome composed of human HLA genes of human MHC loci.

10. The non-human transgenic animal of claim 9, wherein said MHC loci contains all human HLA genes.

11. The non-human transgenic animal of claim 9, wherein said MHC loci contains a portion of human HLA genes.

12. The non-human transgenic animal of any one of claims 9-11, wherein said human HLA genes are MHC class I and MHC class II.

13. The non-human transgenic animal of any one of claims 9-12, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by the human MHC class I receptors and/or reactive to antigen presented by the human MHC class II receptors.

14. The non-human transgenic animal of any one of claims 9-13, wherein said human HLA genes are MHC class I.

15. The non-human transgenic animal of any one of claims 9-14, wherein said human HLA genes are HLA-A2.

16. The non-human transgenic animal of any one of claims 9-15, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by the human MHC class I receptors.

17. The non-human transgenic animal of any one of claims 9-13, wherein said human HLA genes are MHC class II.

18. The non-human transgenic animal of any one of claim 17, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by the human MHC class II receptors.

19. The non-human transgenic animal of any one of claims 9-18, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cell receptors comprise human α and β chains.

20. A non-human transgenic animal of any one of preceding claims, further comprising genes contained within its genome a human co-receptor.

21. The non-human transgenic animal of claim 20, wherein said genes encode a CD8 co-receptor and/or a CD4 co-receptor.

22. The non-human transgenic animal of claim 20 or claim 21, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cell receptors comprise human T-cell receptors and co-receptor molecules.

23. The non-human transgenic animal of any one of claims 20-22, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by human MHC class I receptors and/or reactive to antigen presented by human MHC class II receptors.

24. The non-human transgenic animal of any one of claims 20-23, wherein said co-receptor is a CD8 co-receptor.

25. The non-human transgenic animal any one of claims 20-24, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cell express on their cell surface human T-cell receptors and co-receptor CD8 molecules.

26. The non-human transgenic animal of any one of claims 20-25, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by human MHC class I receptors.

27. The non-human transgenic animal of any one of claims 20-23, wherein said co-receptor is a CD4 co-receptor.

28. The non-human transgenic animal of any one of claims 20-23 and 27, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cells express on their cell surface human T-cell receptors and co-receptor CD4 molecules.

29. The non-human transgenic animal of any one of claims 20-23, 27 and 28, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by human MHC class II receptors.

30. The non-human transgenic animal of any one of the preceding claims, wherein said animal is any animal which can be manipulated transgenically.

31. The non-human transgenic animal of any one claims 1-30, wherein said animal is a mouse.

32. The non-human transgenic animal of any one of claims 1-30, wherein said animal is a rat.

33. The non-human transgenic animal of any one of claims 1-30, wherein said animal is a primate.

34. The non-human transgenic animal of any one of claims 1-30, wherein said animal is a chimpanzee.

35. The non-human transgenic animal of any one of claims 1-30, wherein said animal is a goat.

36. The non-human transgenic animal of any one of claims 1-30, wherein said animal is a pig.

37. The non-human transgenic animal of any one of claims 1-30, wherein said animal is a zebrafish.

38. A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell;

inserting transgenes containing active human T-cell receptor loci in said embryo or embryonic stem cell;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene wherein the animal is capable of producing T-cells that express human T-cell receptors; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

39. The method of claim 38 wherein said endogenous T-cell receptor loci are α and β chain T-cell receptor loci.

40. The method of claim 38 or claim 39 wherein said transgenes comprise human α chain and human β chain T-cell receptor loci.

41. A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell, wherein said loci are T-cell receptor α or T-cell receptor β loci;

producing a transgenic animal from said embryo or embryonic stem cell which contains inactivated loci wherein the animal is incapable of expressing said endogenous loci;

crossing a produced transgenic animal having inactivated endogenous T-cell receptor α loci with a produced transgenic animal having inactivated endogenous T-cell receptor β loci;

selecting progeny having both inactivated endogenous T-cell receptor α and T-cell receptor β loci;

inserting transgenes containing active human T-cell receptor loci in an embryo or embryonic stem cell wherein said human T-cell receptor loci are human T-cell receptor α or T-cell receptor β loci;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene;

crossing a produced transgenic animal having active human T-cell receptor α transgenes with a produced transgenic animal having active human T-cell receptor β transgenes;

selecting progeny having both active human T-cell receptor α and T-cell receptor β transgenes wherein the animal is capable of producing T-cells that express human T-cell receptors;

crossing a produced transgenic animal having both inactivated endogenous T-cell receptor α and T-cell receptor β loci with a produced transgenic animal having both active human T-cell receptor α and T-cell receptor β transgenes;

selecting progeny having inactivated endogenous T-cell receptor α and T-cell receptor β loci and containing active human T-cell receptor α and T-cell receptor β transgenes; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

42. The method of any one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by a functional limitation of the loci.

43. The method of any one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by deleting J segment genes from said loci.

44. The method of any one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by deleting D segment genes from said loci.

45. The method of any one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by deleting C segment genes from said loci.

46. The method of any one of claims 38-45 wherein said human T-cell receptor loci are unrearranged.

47. The method of any one of claims 38-46 wherein said transgenes containing the active human T-cell receptor loci comprise, in operable linkage, a plurality of human T-cell receptor V genes, and D and/or J and C genes.

48. A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors and heterologous MHC molecules, comprising the steps of:

crossing a transgenic animal expressing heterologous T-cell receptors produced by the method of any one of claims 38-47 with a transgenic animal containing human MHC loci and expressing human MHC molecules;

selecting progeny transgenic animals which express heterologous T-cell receptors and heterologous MHC molecules; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors and heterologous MHC molecules.

49. The method of claim 48, wherein said MHC loci contains all human HLA genes.

50. The method of claim 48 wherein said MHC loci contains a portion of human HLA genes.

51. The method of any one of claims 48-50 wherein said human HLA genes are MHC class I and MHC class II.

52. The method of any one of claims 48-51 wherein said human HLA genes are MHC class I.

53. The method of any one of claims 48-51 wherein said human HLA genes are MHC class II.

54. A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors, heterologous MHC molecules, and heterologous co-receptor molecules, comprising the steps of:

crossing a transgenic animal expressing heterologous T-cell receptors and heterologous MHC molecules produced by the method of any one of claims 48-53 with a transgenic animal containing a heterologous co-receptor genes;

selecting progeny transgenic animals which express heterologous T-cell receptors, heterologous MHC molecules, and heterologous co-receptor molecules; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors, heterologous MHC molecules, and heterologous co-receptor molecules.

55. The method of claim 54, wherein said heterologous co-receptor is a CD8 co-receptor and a CD4 co-receptor.

56. The method of claim 54 wherein said heterologous co-receptor is a CD8 co-receptor.

57. The method of any one of claims 54 wherein said heterologous co-receptor is a CD4 co-receptor.

58. An immortal cell line capable of producing heterologous T-cell receptors.

59. The immortal cell line of claim 58 wherein said T-cell receptors are specific for a particular antigen.

60. The immortal cell line of claim 58 or 59 wherein said T-cell receptors are capable of reacting with a chosen peptide/MHC complex of interest.

61. An isolated nucleic acid sequence produced by the cell line of any one of claims 58-60 wherein said sequence encodes or is complementary to a sequence that encodes a heterologous T-cell receptor α or β chain.

62. An isolated nucleic acid sequence produced by the cell line of any one of claims 58-60 wherein said sequence encodes or is complementary to a sequence that encodes a heterologous T-cell receptor α chain.

63. An isolated nucleic acid sequence produced by the cell line of any one of claims 58-60 wherein said sequence encodes or is complementary to a sequence that encodes a heterologous T-cell receptor β chain.

64. The isolated nucleic acid of any one of claims 61-63 wherein the nucleic acid is RNA.

65. The isolated nucleic acid of any one of claims 61-63 wherein the nucleic acid is DNA.

66. Heterologous T-cell receptors produced by the cell line of any one of claims 58-60.

67. The heterologous T-cell receptors of claim 66 wherein the receptors are purified or partially purified.

68. A method of generating an immortal cell line capable of producing heterologous T-cell receptors, comprising the steps of:

producing a transgenic animal capable of producing heterologous T-cell receptors by the method of any one of claims 38-57;

inducing an immune response in said animal;

isolating a T-cell expressing human T-cell receptors; and

fusing the isolated T-cell with an immortalizing cell line to generate an immortal cell line capable of producing heterologous T-cell receptors.

69. The method of claim 68 wherein said isolated T-cell expresses TCR specific for a particular antigen of interest.

70. The method of claim 68 or claim 69 wherein said isolated T-cell expresses TCR capable of reacting with a chosen peptide/MHC complex of interest.

71. The method of any one of claims 68-70 wherein said immortalizing cell line is a myeloma cell line.

72. An isolated nucleic acid comprising a yeast artificial chromosome operably linked to a human T-cell receptor locus.

73. The isolated nucleic acid of claim 72 wherein said human T-cell receptor locus is the α locus.

74. The isolated nucleic acid of claim 72 or claim 73 wherein said α locus comprises Vα genes, Jα genes and Cα genes.

75. The isolated nucleic acid of any one of claims 72-74 further comprising the regulatory sequences of the α locus.

76. The isolated nucleic acid of any one of claims 72-75 further comprising the enhancer region of the α locus.

77. The isolated nucleic acid of any one of claims 72-76 further comprising recombination signals of the α locus.

78. The isolated nucleic acid of any one of claims 72-77 further comprising the promoter region of the α locus.

79. The isolated nucleic acid of any one of claims 72-78 wherein the genes are unrearranged.

80. The isolated nucleic acid of any one of claims 72-79 wherein further comprising the regulatory sequences from a heterologous α locus.

81. The isolated nucleic acid of any one of claims 72-80 wherein further comprising the enhancer region from a heterologous α locus.

82. The isolated nucleic acid of any one of claims 72-81 wherein further comprising the promoter region of a heterologous α locus.

83. The isolated nucleic acid of claim 72, wherein said human T-cell receptor locus is the β locus.

84. The isolated nucleic acid of claim 72 or claim 83, wherein said β locus comprises Vβ genes, Dβ genes, Jβ genes and Cβ genes.

85. The isolated nucleic acid of any one of claims 72, 83 or 84 further comprising the regulatory sequences of the β locus.

86. The isolated nucleic acid of any one of claims 72 or 83-85 further comprising the enhancer region of the β locus.

87. The isolated nucleic acid of any one of claims 72 or 83-86 further comprising recombination signals of the β locus.

88. The isolated nucleic acid of any one of claims 72 or 83-87 further comprising the promoter region of the β locus.

89. The isolated nucleic acid of any one of claims 72 or 83-88 wherein the genes are unrearranged.

90. The isolated nucleic acid of any one of claims 72, 83-89 wherein further comprising the regulatory sequences from a heterologous TCRβ gene.

91. The isolated nucleic acid of any one of claims 72 or 83-90 further comprising the enhancer region of a heterologous β locus.

92. The isolated nucleic acid of any one of claims 72 or 83-91 further comprising the promoter region of a heterologous β locus.

93. An isolated nucleic acid comprising a yeast artificial chromosome operably linked to a human MHC locus.

94. The isolated nucleic acid of claim 93 wherein said MHC locus comprises a human HLA class I locus.

95. The isolated nucleic acid of claim 93 or claim 94 wherein said MHC locus comprises all human HLA class I genes.

96. The isolated nucleic acid of claim 93 or claim 94 wherein said MHC locus comprises a portion of human HLA class I genes.

97. The isolated nucleic acid of any one of claims 93-96 wherein said MHC locus is human HLA-A2 gene.

98. The isolated nucleic acid of claim 93 wherein said MHC locus comprises a human HLA class II locus.

99. The isolated nucleic acid of claim 93 or claim 98 wherein said MHC locus comprises all human HLA class II genes.

100. The isolated nucleic acid of any one of claims 93, 98 or 99 wherein said MHC locus comprises a portion of human HLA class II genes.

101. An isolated nucleic acid comprising a promoter operably linked to a heterologous co-receptor gene.

102. The isolated nucleic acid of claim 101 wherein said heterologous co-receptor gene is a CD4 co-receptor.

103. The isolated nucleic acid of claim 101 wherein said heterologous co-receptor gene is a CD8 co-receptor.

104. The isolated nucleic acid of claim 101 or claim 103 wherein said CD8 co-receptor is composed of α and β chains.

105. An isolated nucleic acid comprising a targeting vector containing a drug selection marker having targeting sequences homologous to 5' and 3' sequences of an endogenous locus of interest.

106. The isolated nucleic acid of claim 105 further comprising a Herpes Simplex Virus thymidine kinase gene cassette.

107. The isolated nucleic acid of claim 105 or claim 106 wherein the targeting sequences are capable of directing homologous recombination at the endogenous locus.

108. The isolated nucleic acid sequence of any one of claims 105-107 wherein homologous recombination at the endogenous locus results in functional inactivation at the endogenous locus.

109. The isolated nucleic acid of any one of claims 105-108 wherein the targeted sequences are endogenous T-cell receptor loci.

110. The isolated nucleic acid of any one of claims 105-109 wherein the targeted sequences are endogenous α chain T-cell receptor loci.

111. The isolated nucleic acid of any one of claims 105-110 wherein the targeted sequences are endogenous β chain T-cell receptor loci.

106. A non-human transgenic animal comprising inactivated endogenous T-cell receptor gene loci, said transgenic animal further containing in its genome transgenes comprising, in operable linkage, a plurality of human T-cell receptor V genes, and their D and /or J and C genes.

107. A non-human transgenic animal having a germline genome with:

a human T-cell receptor β chain transgene comprising in operable linkage a plurality of human V genes, and either one or both of the Cβ loci and wherein in lymphocytes of said non-human transgenic animal the transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human β chain in detectable amounts in response to antigenic stimulation;

a human T-cell receptor α chain transgene with plurality of human V gene segments, human J gene segments, the human Cα coding exon, and a human 3' downstream α enhancer; and wherein in lymphocytes of said non-human

transgenic animal the transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human α chain in detectable amounts in response to antigenic stimulation;

an endogenous TCR β chain loci having an inactivated β chain gene; and

an endogenous TCR α chain loci having an inactivated α chain gene.